

# Two boundary model for freezing front propagation in biological tissue

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## Abstract

The response of the living tissue to the effects of strong heating or cooling can cause the blood flow rate to vary by an order of magnitude. A mathematical model for the freezing of living tissue is formulated which takes into account the nonlocal temperature dependence of the blood flow rate when the temperature distribution in the tissue is substantially nonuniform, as in cryosurgery.

## INTRODUCTION

Mathematical analysis and prediction of temperature distribution in living tissue during the process of freezing has been used in the study and optimization of cryosurgical procedures. In the last years a number of different approaches to describing the heat transfer process in living tissue have been proposed (for a review see[1]–[15]). Within the framework of these approaches the obtained bioheat equation is of the

$$c\rho\frac{\partial T}{\partial t} = \nabla(k\nabla T) - c_b\rho_b Jf(T - T_a) + S, \quad (1)$$

where  $T$  is the tissue temperature,  $c$  and  $\rho$  denote the specific heat and density of the tissue,  $c_b$  and  $\rho_b$  are the specific heat and density of blood,  $J$  is the blood flow rate per unit tissue evolume, (i.e. the volume of blood flowing through a unit volume of tissue per unit time),  $k$  is the thermal conductivity of the tissue [14],[15],  $T_a$  is the systemic arterial blood temperature and  $S$  is the rate of metabolic heat generation. Cofactor  $f$ , ranging from 0 to 1 is due to heat exchange between arterial and venous blood flowing through the nearest vessels[5]–[10].

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Propagation of the freezing front  $\Gamma$  is conventionally described in terms of the free boundary problem of the Stefan-type [3]:

$$v_n \rho L = -(k \nabla_n T) |_{\Gamma_+} + (k \nabla_n T) |_{\Gamma_-} , \quad (2)$$

$$T |_{\Gamma_+} = T |_{\Gamma_-} = T_f , \quad (3)$$

where  $L$  is the latent heat of fusion,  $\Gamma_+$  and  $\Gamma_-$  denote the boundaries of the freezing front on the living and frozen sides of the tissue, respectively, and  $T_f$  is the freezing temperature (fig.1).

A more accurate description of the heat transfer process in living tissue is obtained if one takes into account the fact that living tissue form an active, highly heterogeneous medium. In particular, the phase transition in living tissue does not occur at a single temperature, but over a temperature range. The influence of this effect has been investigated in [1]. Also, when the size of the frozen region of the tissue is small in comparison with the characteristic length of the blood vessels that directly control the heat exchange between the cellular tissue and blood, the heterogeneity of living tissue has a substantial effect on the heat transfer process. Therefore, equation (1) which models the blood flow rate in terms of a continuous field  $J(\mathbf{r})$  has to be modified.

The response of the living tissue to the effects of strong cooling or strong heating can cause the blood flow rate to vary by an order of magnitude [11]. In general, if the temperature distribution in the tissue is substantially nonuniform, as for example in cryosurgery, then the temperature dependence of the blood flow rate is nonlocal and the blood flow rate at a given point depends on certain characteristics of the temperature distribution rate, other than the tissue temperature at the point only. Indeed, variations in the blood flow rate at a given point are caused mainly by the overall response of the blood collection vessels, involving arteries of different length and radius. Hence, equation (1) should be modified to include a relationship specifying the tissue temperature dependence on the blood flow rate [5].

In this paper we shall formulate a phenomenological model for the thermal response in living tissue during the freezing process that will include the effects of the aforementioned factors. It should be pointed out that the main equations to be formulated can be obtained by rigorous analysis of the microscopic relations governing the heat transfer process in living tissue and the response of the vascular network, which we shall consider in a subsequent paper.

## TWO BOUNDARY MODEL

Let us assume that all characteristic scales of the temperature distribution over the living tissue are greater than the mean length  $l_v$  of the vessels that directly control the heat exchange between the cellular tissue and blood. In this case equation (1) is actually the result of averaging over the scale  $l_v$  the microscopic equation describing heat exchange between blood in different vessels and the cellular tissue. Therefore, the quantity  $J$  appearing in equation (1) is actually the blood flow rate averaged on the scale  $l_v$ , rather than the true blood flow rate  $J_t$ .

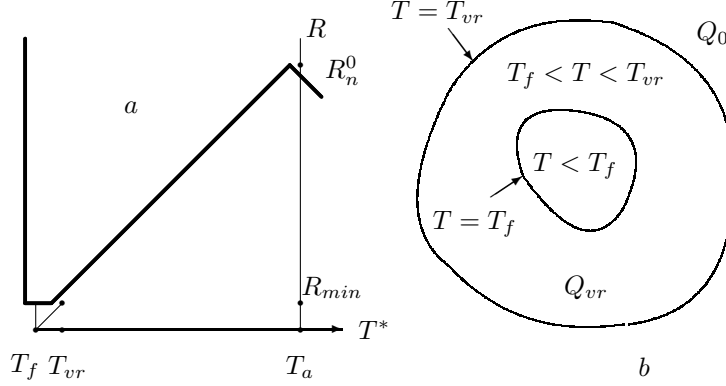


Figure 1: Two boundary model for tissue freezing processes: a - the vessel resistance as a function of the blood temperature, b - characteristic region of living tissue.

Nonuniformity in the true blood flow rate  $J_t$  can be explicitly associated with the distortion of the vascular network and, therefore, can be characterized by scales much less than  $l_v$ . On scales substantially larger than  $l_v$  the averaged blood flow rate and the true blood flow rate coincide, leading to the identity  $J = J_t$ . On scales less than  $l_v$ , the averaged blood flow rate obeys the conservation law for the total blood flow.

A simplest relation that allows for the features mentioned above can be expressed in the form[5]-[10]

$$J - \nabla(l_c^2 \nabla J) = J_t. \quad (4)$$

The form of the second term on the left-hand side of (4) follows from the requirement that its integral over the whole tissue domain under consideration should be equal to zero. The mean length  $l_c$  of the vessels controlling the heat transfer between blood and the cellular tissue in a given domain of radius  $l_v$  is determined by the mean blood flow in this domain, i.e., by the averaged blood flow rate  $J$ .

To find the relationship between  $l_v$  and  $J$ , let us consider the heat transfer in a given domain of diameter  $l$ . We assume that such a domain, on the average, contains one artery (arteriole) and one vein (venule) of length  $l$ , which is typical is the case of living tissues [11]. The characteristic rate of heat generation (or dissipation) in a domain due to convective blood flow in these vessels can be estimated as  $c_b \rho_b (T^* - T_a) \pi a^2 v$ , where  $T^*$  and  $v$  are the mean temperature and velocity of blood in the vessels and  $a$  is their radius. Similarly, the characteristic rate of heat generation due to heat conduction in living tissue is given approximately by  $c \rho (T - T_a) V \cdot k / (\rho c l^2)$ , where  $V \sim l^3$  is the volume of the domain, and  $l^2 c \rho / k$  is the characteristic time of temperature variation on the scale  $l$ , caused by heat conduction. On the scale  $l_c$  the two quantities should be of the

same order, i.e.

$$c\rho(T^* - T_a) V_c \left( \frac{l_c^2 c\rho}{k} \right)^{-1} \sim c_b \rho_b (T - T_a) \pi a^2 v$$

and the blood temperature in the corresponding vessels must be in thermodynamic equilibrium with the cellular tissue, i.e.,  $T^* \sim T$ . Taking into account that  $J \sim \pi a^2 v / V_c$  and  $c\rho \sim c_b \rho_b$  we obtain

$$l_c^2 \approx \frac{k}{\rho c} \cdot \frac{1}{J} . \quad (5)$$

In particular, for typical values of  $k/\rho c \sim 2 \cdot 10^{-3} \text{ cm}^2/\text{s}$  and  $J \sim 3 \cdot 10^{-3} \text{ s}^{-1}$  it follows from (5) that  $l_c \sim 1 \text{ cm}$ .

Given the true blood flow rate  $J_t$ , (equation (1),(4)) and the relation (5) determine the temperature distribution in living tissue. In order to complete the model we must describe the response of the vascular network to the tissue temperature variation. Since the heat exchange between cellular tissue and blood in the vessels of length larger than  $l_c$  is negligibly small [11], the convective heat flow through such vessels obeys the conservation law. Therefore, the heat flow  $c_b \rho_b (T_i^* - T_a) I_i$  ( $I_i = \pi (a^2 v)_i$ ) in a vein  $i$  of length  $l > l_c$  is approximately equal to the total heat dissipation rate due to blood flow in the domain  $Q_i$ , which is directly supplied with blood through this vein and the corresponding artery. In other words, for such a vein  $i$  we have

$$c_b \rho_b (T_i^* - T_a) I_i = \int_{Q_i} d\mathbf{r} c_b \rho_b J (T - T_a) ,$$

where the averaged blood flow rate  $J$  can be replaced by the true rate  $J_t$ , since  $l \gg l_v$ . Upon substitution, this equation is valid formally for veins whose length  $l < l_v$ . Indeed, in this case it reduces to the identity

$$I_i = \int_{Q_i} J_t d\mathbf{r} \quad (6)$$

and blood in such a veins is in the thermodynamic equilibrium with cellular tissue, i.e.  $T_i^* \simeq T$ . Thus, for any vein  $i$  we may write

$$(T_i^* - T_a) I_i = \int_{Q_i} d\mathbf{r} J_t (T - T_a) . \quad (7)$$

A valid response of the vascular network to temperature variation requires that the resistance of each artery  $i$  should depend on the mean tissue temperature in the domain  $Q_i$ , rather than on particular details of temperature distribution over the domain  $Q_i$ . Taking into account equation (7), it is natural to assume that an artery  $i$  responds to the temperature  $T_i^*$  of the blood in a vein

$i$ , because the value of  $T_i^*$  can be treated as a mean tissue temperature in the corresponding domain  $Q_i$ . In other words, at least in the quasistationary case, we may suppose that the resistance  $R_i$  to blood flow in a vein  $i$  is an explicit function of  $(T_i^* - T_a)$ .

The blood flow distribution  $\{I_i\}$  over the vascular network is directly determined by the vascular network architectonics and total pressure drop across it, provided all the vessel resistances are have given. Thus, when the distribution of the temperature dissipation rate  $J_t(T - T_a)$  in the living tissue is a given field, the explicit dependence of the blood temperature  $T_i^*$  in the vein  $i$  on the blood flow  $I_i$  (through the dependence of the vessel resistances on the blood temperature, see (7)) completely determines the blood flow pattern  $\{I_i\}$ . In other words, the temperature dissipation rate can be treated as the information field for the thermoregulation of living tissue.

Hence, in the general case the evolution equation for the true blood flow rate may be represented as

$$\tau \frac{\partial J_t}{\partial t} + J_t = J_0 + F\{J_t(T - T_a)\} , \quad (8)$$

where the transient term allows for a possible time delay  $\tau$  in the vascular network response to the temperature variations,  $J_0$  is a uniform blood flow rate when  $T = T_a$  and  $F\{J_t(T - T_a)\}$  is certain functional operator of the information field  $J_t(T - T_a)$  that specifies thermoregulation in the living tissue. The simplest expression for the response operator  $F$ , which models thermoregulation correctly may be written in the form

$$F\{J_t(T - T_a)\} = \frac{1}{\Delta} \int_{Q_0} d\mathbf{r}' G(\mathbf{r}, \mathbf{r}') J_t(\mathbf{r}') [T(\mathbf{r}') - T_a] , \quad (9)$$

where  $Q_0$  is the total living tissue domain under consideration,  $G(\mathbf{r}, \mathbf{r}')$  is the kernel of the operator  $F$ ,  $\mathbf{r}$  and  $\mathbf{r}'$  are vectors, and  $\Delta$  is the length of temperature survival of the living tissue, in particular  $\Delta \approx T_a - T_f$ . Typically, the temperature response of the vessels within a tumor is strongly depressed. This allows us to set

$$G(\mathbf{r}, \mathbf{r}') = 0 , \quad (10)$$

where the point  $\mathbf{r}'$  belongs to the tumor domain  $Q_t$ , i.e.  $\mathbf{r}' \in Q_t$ . When the tissue temperature attains a certain low value  $T_{vr} > T_f$ , the vessels exhaust their ability to respond to temperature variation and the blood flow rate is no longer dependent on the tissue temperature. In mathematical terms this effect can be taken into account if in the response operator  $F\{J_t(T - T_a)\}$  the true tissue temperature  $T$  is replaced by a seeming tissue temperature  $T_s$ , which coincides with the true tissue temperature  $T$  when  $T > T_{vr}$  and is equal to  $T_{vr}$  for  $T_f < T < T_{vr}$ . Thus, for the given linear response operator (9) the temperature response of the vascular network may be described by the equation with saturation by the following equation

$$\tau \frac{\partial J_t}{\partial t} + J_t = J_0 + \frac{1}{\Delta} \int_{Q_0} d\mathbf{r}' G(\mathbf{r}, \mathbf{r}') J_t(\mathbf{r}') [T_s(\mathbf{r}') - T_a] , \quad (11)$$

where

$$T_s = \begin{cases} T & \text{if } T > T_{vr} \\ T_{vr} & \text{if } T_f \leq T \leq T_{vr} \end{cases} . \quad (12)$$

In the frozen region  $Q_f$  where  $T < T_f$

$$J_t = 0 . \quad (13)$$

The system of equations (1),(4),(11) with boundary conditions (2),(3) and relations (12),(13) form the desired complete phenomenological model for the freezing process of living tissue. It should be pointed out that, within the framework of the proposed model, the living tissue freezing process may be represented by the propagation of two boundaries, which divide the tissue into three regions. The first one is the frozen region, which is separated from the extremely cooled tissue region (the second region) by the interface  $\Gamma$  where  $T = T_f$ . In the extremely cooled region the temperature self-regulation is depressed and an effective boundary of seeming temperature separates it from the third region, where the temperature varies significantly in the presence of high blood flow rate.

To complete the description of our model for the freezing processes of living tissue we need to specify the kernel  $G(\mathbf{r}, \mathbf{r}')$ . The kernel should account for two different effects. The first of these is an increase in the blood flow rate at the point  $\mathbf{r}$ , associated with additional blood flow coming from systematic circulation through the host artery of the vascular network. The second effect is the redistribution of the available blood flow in the vascular network. However, when the resistance to blood flow in the vascular network is determined by a group of vessels that are very great in length, then the thermoregulation processes will give rise to the formation of a low resistance path on the vascular network that connects the host artery and the small arteries located in the region of considerable temperature increase. In this case the blood flow redistribution effect is ignorable in comparison with the first effect mentioned above, and the kernel  $G(\mathbf{r}, \mathbf{r}')$  may be represented approximately by the  $\delta$ -function

$$G(\mathbf{r}, \mathbf{r}') \approx \delta(\mathbf{r} - \mathbf{r}') \Theta_+(\mathbf{r}') . \quad (14)$$

where  $\Theta_+ = 0$  if  $\mathbf{r} \in Q_t$  and  $\Theta_+ = 1$  for  $\mathbf{r} \notin Q_t$ .

By definition, the thermal self-regulation process, where the kernel  $G(\mathbf{r}, \mathbf{r}')$  is represented by the expression (14), is called ideal thermoregulation.

For ideal thermoregulation, equation (11) takes the following form for the unfrozen region [5]-[9]

$$\tau \frac{\partial J_t}{\partial t} + \left( \frac{T_f - T}{T_f - T_a} \right) J_t = J_0 , \quad (15)$$

when  $T < T_{vr}$  and  $\mathbf{r} \notin Q_t$ , for  $\mathbf{r} \in Q_t$

$$J_t = J_0 . \quad (16)$$

In the extremely cooled region, where  $T_f < T < T_{vr}$  and for  $\mathbf{r} \notin Q_t$

$$J_t = J_0 \frac{T_f - T_a}{T_f - T_{vr}} . \quad (17)$$

Thus, for ideal thermoregulation the description of the freezing process for living tissue is reduced to the system of equation (1),(4),(15), the boundary conditions (2),(3) and the expressions (14),(16),(17). It should be noted that in this model the frozen region and the region where the blood flow rate strongly depends on temperature are separated by a layer (the extremely cooled region) where the blood flow rate has the maximum and is independent of the tissue temperature.

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